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Collapsing glomerulopathy in HIV and non-HIV patients: A clinicopathological and follow-up study

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Collapsing glomerulopathy in HIV and non-HIV patients: A clinicopathological and follow-up study.

Background. Collapsing glomerulopathy (CG) is a pattern of renal injury that is seen in association with HIV infection and that is increasingly recognized in non-HIV patients.

Methods. A review of native kidney biopsies with CG that were diagnosed between 1979 and 1997 in 18 HIV and 42 non-HIV patients is provided.

Results. HIV and non-HIV patients with CG were similar in terms of age, sex ratio, serum creatinine, proteinuria, the extent of collapsing and sclerosing glomerular lesions, and interstitial damage. A slight female predominance was found in both groups. In contrast to non-HIV patients, the HIV group was characterized by a high prevalence of blacks (94 vs. 57%), frequent tubuloreticular inclusions (76 vs. 29%), and microcystic tubular changes (72 vs. 40%). In 13 non-HIV patients, CG was associated with a systemic lupus erythematosus (SLE)-like disease (5), hepatitis C virus (HCV) infection (3), HTLV-I infection, MCTD, acute monoblastic leukemia, multiple myeloma, and cerebral arteritis. Overall, the renal survival of human immunodeficiency virus (HIV) and non-HIV patients with CG was not significantly different. Cox regression revealed that HIV infection had an adverse effect on short-term renal survival, with other significant risk factors being extensive interstitial fibrosis, high serum creatinine, proteinuria, and a low percentage of glomeruli with collapse. The slope of reciprocal creatinine was best predicted by the degree of proteinuria. Serum creatinine correlated with the extent of interstitial fibrosis, the male gender, and the percentage of glomeruli with collapse. Proteinuria was best predicted by the extent of effacement of podocyte foot processes.

Conclusions. CG shares many clinicopathological similarities in HIV and non-HIV patients. In some non-HIV patients, CG was associated with autoimmune diseases, lymphoproliferative disorders, and viral infections.

With the advance of the epidemic of acquired immunodeficiency syndrome (AIDS) in the Western world in late 1970s, a new type of renal injury emerged. AIDS-associated nephropathy, characterized by focal and segmental glomerulosclerosis (FSGS) with massive proteinuria and rapid progression to end-stage renal disease (ESRD), was recognized as a frequent pattern of renal disease in these patients [1, 2]. Other studies confirmed unique clinical and pathologic features of this condition, and eventually, it became known as HIV-associated nephropathy (HIVAN), emphasizing the collapsing features of glomerular damage along with frequent tubular and interstitial involvement by severe degenerative and inflammatory changes [3–10]. HIVAN has also been regarded by some authors to have certain distinct features compared with heroin-associated nephropathy (HAN) [1, 3, 7, 9, 11]. Furthermore, although HIVAN initially appeared to be associated with intravenous drug abuse (IVDA) as a mode of HIV transmission, later observations revealed that this association was due to a high prevalence of blacks with HIVAN rather than to IVDA itself [3, 4, 12–14].

In 1986, Weiss et al reported six patients with rapidly progressive nephrotic syndrome and glomerular capillary collapse [15]. Because only one of these patients subsequently developed AIDS, these authors suggested that this condition may represent a new clinicopathological entity. As a matter of fact, pathologic features of this entity closely resembled the pathology of HIVAN [9]. Later studies confirmed the existence of collapsing glomerulopathy (CG) independent of HIV infection (no evidence of HIV-1 infection or risk factors for HIV) [16–18]. These studies also showed that CG represents an aggressive form of renal disease when compared with the more classic histological type of idiopathic focal segmental glomerulosclerosis (FSGS).

Although the existence of idiopathic CG independent of HIVAN, HAN, and classic idiopathic FSGS is well recognized, it remains unclear what factors contribute to the occurrence of this form of glomerular injury and why this renal condition seems to have emerged in parallel to the epidemic of HIV-1 infection. It is also unclear

Key words: acquired immunodeficiency syndrome, progressive renal disease, glomerulosclerosis, human immunodeficiency virus, infection.

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whether idiopathic CG has distinct demographic, clinical, pathological, and prognostic features when compared with HIVAN. Therefore, we designed our study to investigate the whole spectrum of CG as a pattern of renal injury, and to contrast features of this condition in patients with and without HIV infection.

METHODS

Material

Renal biopsies received by the Department of Pathology of the Brigham and Women's Hospital (BWH) from 1979 to January 1997 with established or potential diagnosis of CG regardless of patients' HIV status were identified. These biopsies were then re-examined, and the cases were classified as CG when focal segmental and/or global collapse of the glomerular capillary tuft was present, as described previously [15–17]. At least one glomerulus with characteristic features of segmental or global capillary collapse, with wrinkling of the basement membrane, prominence and crowding of the epithelial cells, and frequent protein reabsorption droplets, was required for the diagnosis of CG. The results of immunofluorescence microscopy and electron microscopy were again reviewed, and some electron microscopy specimens were re-examined when necessary. A total of 63 native kidney biopsies reviewed satisfied the diagnostic criteria for CG.

Light microscopy slides that were examined contained at least 6 glomeruli per section (median of 17). The percentage of globally/segmentally collapsed and globally sclerosed glomeruli was calculated. The presence of tubular casts with microcystic dilation was noted. The degree of active interstitial inflammation and interstitial fibrosis was estimated as a percentage of the cortical area involved. The degree of effacement or "fusion" of glomerular epithelial cell foot processes was estimated semiquantitatively as focal for $<50\%$, extensive for 50 to 80%, and diffuse for $>80\%$ of the glomerular capillaries revealing this feature. The presence of tubuloreticular inclusions (TRIs) was noted in the glomerular endothelial cells.

Clinical information on the patient at the time of the biopsy as well as follow-up data was obtained from the biopsy record, clinical histories, and questionnaires submitted to the nephrologists following the patients. Data on testing for HIV were also retrieved under authorized permission from the Department of Laboratory Medicine of BWH. Information on some patients' human lymphocyte antigen (HLA) phenotype was available at the Immunogenetics Laboratory at BWH.

Patients were defined as HIV positive according to the results of HIV-1 and HIV-2 serologic testing. Seventeen patients tested positive for HIV-1, and one patient was found to have HIV-2 infection. Eight HIV-1–positive patients tested negative for HIV-2. The time of positive HIV test performed with respect to the renal biopsy was variable: Six patients tested positive before the biopsy, five at the time of biopsy, and seven after the biopsy findings suggested the possibility of HIV infection. The patients diagnosed as being HIV positive after the biopsy were also considered as having CG associated with HIV infection.

Non-HIV patients were defined as either having negative HIV test results (36 patients) or not having risk factors for HIV infection and not having developed features of AIDS during the follow-up period (6 patients). Eighteen of the 36 HIV-1–negative patients also tested negative for HIV-2.

Three patients were excluded from further analysis because of inadequate information to define the HIV status.

Risk factors for HIV infection were defined as history of IVDA, male homosexuality, or engaging in unprotected sex known before or after the diagnosis of CG.

Statistical methods

Groups were compared using Fisher's exact test for dichotomous data, Wilcoxon rank-sum tests for ordinal data, and *t*-tests for approximately normally distributed data. Multiple regression was used to develop models to predict proteinuria, serum creatinine, and the slope of reciprocal creatinine. Product-limit estimates were used to summarize renal survival data, and the log rank test was used for comparing renal survival distributions [19]. Renal death was defined as the initiation of permanent renal replacement therapy, and renal survival was defined as the time from renal biopsy to renal death. Cox proportional hazards analysis was used to develop a multiple variable model to predict the time to renal death [20]. A combination of forward, backward, and stepwise procedures was used to arrive at the final model [21]. A term representing the interaction of HIV status and time was added to the model after observing that the hazard ratio for HIV was not constant. The rate of progression of renal insufficiency was defined as the slope of reciprocal serum creatinine, produced by best-fit regression analysis using an inverse creatinine as the dependent variable and the time of the measurement of the serum creatinine as an independent variable (minimum of 4 time points). Numerical variables are represented as the arithmetic mean $\pm$ SD.

RESULTS

Comparison of demographic, clinical, and pathological characteristics of collapsing glomerulopathy in HIV and non-HIV patients

A slight predominance of female sex was observed in both groups (Table 1). The male-to-female ratio was 0.80 and 0.83 in the HIV and non-HIV groups, respectively. There was a significant predominance of blacks in the

Table 1. Demographics of collapsing glomerulopathy (CG) in HIV and non-HIV patients

	HIV ($N = 18$)	Non-HIV ($N = 42$)	P value
Gender *% female*	56%	55%	1.0[a]
Race *% black*	94%	57%	0.005[a]
Age at biopsy *median (range)*	36.0 (26–70)	38.5 (13–77)	0.5[b]

[a] By Fisher's exact test
[b] By Wilcoxon rank sum analysis

Table 2. Prevalence of identified risk factors in HIV and non-HIV patients

	HIV ($N = 18$)	Non-HIV ($N = 42$)	P value
History of any potential risk factor for HIV	72%	19%	0.0002
IVDA	44%	12%	0.013
Male homosexual	11%	2%	0.2
History of unprotected sex	17%	5%	0.15

IVDA is intravenous drug abuse. P values are by Fisher's exact test.

Table 3. Clinical characteristics of CG in HIV and non-HIV patients

Characteristic	HIV	N	Non-HIV	N	P value
Time to biopsy *months, median*	0.75	17	1	38	0.6[a]
Proteinuria at biopsy *g/day, median*	8.7	17	11.8	36	0.2[a]
Serum creatinine at biopsy *mg/dl, median*	3.5	17	2.9	40	0.2[a]
Creatinine >2.0 mg/dl, at biopsy, %	76%	17	70%	40	0.8[b]
Nephrotic proteinuria at presentation	78%	18	89%	38	0.3[b]
Renal failure at presentation	72%	18	74%	38	1.0[b]
Hypertension at presentation	6%	18	29%	38	0.004[b]
Flu-like illness at presentation	14%	14	26%	38	0.5[b]
Vomiting at presentation	14%	14	29%	38	0.5[b]
Diarrhea at presentation	21%	14	11%	38	0.4[b]
Fever at presentation	50%	14	16%	38	0.026[b]
Loss of weight at presentation	29%	14	11%	38	0.2[b]

[a] By Wilcoxon rank sum analysis
[b] By Fisher's exact test

HIV group (94%) compared with the non-HIV group (57%, $P < 0.005$). The only non-black HIV patient was of Hispanic ethnicity, and 5 of the 18 white non-HIV patients were Hispanics. Six of the HIV and eight of non-HIV patients were also identified as descendents from inhabitants of the Caribbean islands. The mean age of the HIV and non-HIV patients was 37.0 ± 10.5 and 37.8 ± 14.2 years, respectively.

The history of potential risk factors for HIV was more frequently identified in HIV patients (72 vs. 19% in the non-HIV group, $P = 0.0002$; Table 2). All of the non-HIV patients with a history of risk factors tested negative (most of them repeatedly) for HIV.

The mean duration of renal disease before the biopsy was 3.3 ± 5.2 and 2.3 ± 2.7 months in HIV and non-HIV patients, respectively (Table 3). At the time of the biopsy, the daily urinary protein excretion was on average 10.3 ± 8.5 and 13.3 ± 10.6 g/24 hr, and serum creatinine was 6.0 ± 5.9 and 5.4 ± 5.3 mg/dl in HIV and non-HIV groups, respectively. Similarly, frequencies of main renal and nonrenal manifestations of the disease were not significantly different between the two groups, except higher incidence of reported arterial hypertension in non-HIV patients and higher incidence of fever in HIV patients (Table 3).

The results of serological tests were available in a subset of patients. None of the HIV patients revealed a positive anti-nuclear antibody (ANA) test ($N = 7$), whereas 10 of 31 non-HIV patients showed a positive ANA screening test at titers higher than 1:40. Three of the ANA-positive patients also had anti–double-stranded DNA antibodies. Two non-HIV patients were positive for rheumatoid factor ($N = 13$). No patients, when tested, were positive for anticardiolipin antibodies ($N = 6$), lupus anticoagulant ($N = 3$), or ANCA ($N = 17$).

Of the 18 HIV-positive patients, 2 also were positive for hepatitis B-s-antigen (HBsAg), and 2 were positive for antibodies against hepatitis C virus (HCV), potentially contracted before the initiation of dialysis.

In the non-HIV group, three White patients with a history of IVDA were positive for HCV (2 before the biopsy, and 1 after the biopsy but before initiation of dialysis). One of these three HCV-positive patients was also found to have TRIs on biopsy; nevertheless, he had twice tested negative for HIV-1 and once for HIV-2. Two black intravenous drug abusers were found to be HCV positive while on dialysis (the test for HCV was not available at the time of the biopsy). As a matter of fact, all of the five non-HIV patients with a history of IVDA were HCV positive. Twenty-three patients tested negative for HCV. Thirty-one patients tested negative for HBsAg. Two of them became HBsAg positive after they had developed ESRD. One patient of Haitian origin with repeatedly negative HIV tests and no identified risk factors for HIV was found to have human T cell lymphotropic virus-1 (HTLV-I) infection.

Several patients in the non-HIV group had other medical conditions that by clinical setting could be potentially associated with their renal disease. Five black ANA-positive female patients (including 3 patients with anti-DNA antibodies) had clinical manifestations characterized as a systemic lupus erythematosus (SLE)-like disorder; however, none of them had an established diagnosis of SLE. One Hispanic male patient had been diagnosed with mixed connective tissue disease. One Caucasian female

Table 4. Pathology findings on biopsy

	HIV ($N = 18$)	Non-HIV ($N = 42$)	P value
Mean % of glomeruli with collapsing lesions	45.8 ± 36.2	40.5 ± 29.4	0.6[a]
Mean % of globally sclerosed glomeruli	16.0 ± 17.4	20.5 ± 28.1	0.5[a]
Mean % of affected (collapsed/globally sclerosed) glomeruli	61.8 ± 38.5	61.0 ± 30.9	0.9[a]
Mean % of renal cortex with interstitial inflammation	27.2 ± 22.7	25.2 ± 26.7	0.8[a]
Mean % of renal cortex with interstitial fibrosis	34.2 ± 24.6	30.6 ± 33.4	0.7[a]
Marked cast nephropathy	72%	40%	0.047[b]
TRIs in glomerular endothelial cells	76%[c]	29%[e]	0.0014[b]
Diffuse effacement of podocyte foot processes	57%[d]	38%[f]	0.342[b]

[a] By unpaired *t*-test
[b] By Fisher's exact test
[c] $N = 17$
[d] $N = 14$
[e] $N = 38$
[f] $N = 37$

had multiple myeloma at the time of renal biopsy, which revealed CG but no paraprotein deposition. One African American male died of acute monoblastic leukemia. One 13-year-old Puerto Rican boy died of granulomatous (giant cell) cerebral arteritis confirmed by autopsy findings. All of these patients developed ESRD during the follow-up period except two patients with SLE-like disorders, who died because of complications of their systemic disease.

Light microscopy findings were strikingly similar in both groups (Table 4), except for a significant predominance of microcystic tubular dilation with casts in HIV patients (72 vs. 40% in non-HIV, $P = 0.045$). Interstitial inflammation affected 20% or more of the renal cortex in 61% HIV and 49% non-HIV patients, whereas interstitial fibrosis of more than 20% was seen in 71% of HIV and 46% of non-HIV patients. Cellular crescent formation was seen in one HIV and nine non-HIV patients. The incidence of TRIs in the glomerular endothelial cells found by electron microscopy was significantly higher in the HIV group (76 vs. 29% in non-HIV, $P = 0.0014$). The effacement of podocyte foot processes was estimated as diffuse in only 57 and 38% of the HIV and non-HIV patients, respectively. In addition to morphological findings diagnostic of CG, three cases also revealed features of membranous nephropathy and one case of IgA nephropathy in the non-HIV group, which by morphologic and clinical criteria were interpreted as a chronic underlying glomerular disease with superimposed CG. Interestingly, follow-up of these four patients showed a rather fast progression of renal insufficiency, not characteristic for the underlying glomerular diseases but in keeping with the diagnosis of CG.

Table 5. Multiple variable models to predict serum creatinine and daily proteinuria at biopsy

	Model or partial R^2	Parameter estimate	Standard error	P value
Prediction of serum creatinine ($N = 55$)	0.71			0.0001
% Interstitial fibrosis	0.53	0.05	0.02	0.0031
Male gender	0.13	3.76	0.99	0.0004
% Glomeruli with collapsing lesions	0.05	0.04	0.01	0.0051
Prediction of 24-hour proteinuria ($N = 45$)	0.65			0.0001
Fusion of podocyte foot processes	0.61	5.81	1.41	0.0002
Patient's age	0.04	0.11	0.05	0.0271

As HIV testing was frequently performed after the renal biopsy, prompted by the diagnosis of CG, we questioned the predictive value of the morphologic features of CG seen on biopsy with respect to the patient's HIV status known either before or after the biopsy. The sensitivity of TRIs for prediction of HIV infection was 0.76, and the specificity was 0.71, with a positive predictive value of 0.54 in all patients with CG. Similarly, the presence of casts in the tubules with microcystic dilation had a sensitivity of 0.72 and a specificity of 0.6.

Data on human lymphocyte antigen (HLA)-A and HLA-B frequencies were available on 13 black patients (2 of them were HIV patients) and 7 white (all non-HIV) patients. HLA-DR antigens were identified in 12 black and 7 white patients, respectively. The statistical significance of prevalence of individual antigens in our patients was tested by comparison to the antigen frequencies in reference population, recalculated [$2 * (\text{gene frequency}) - (\text{gene frequency})^2$] from HLA gene frequencies available in the literature [22]. Although observed HLA antigen frequencies did not differ significantly from the control population after a correction of P values by the conservative method of Bonferroni for multiple comparisons, relatively high frequencies of HLA-B18 (23%) and HLA-DR10 (25%) in blacks and HLA-B44 (71%) and HLA-DR4 (57%) in whites were noted. Interestingly, all white patients had either HLA-B44 or HLA-DR4 or both antigens.

Clinical and pathological correlates

Clinical and morphological predictors of serum creatinine and daily proteinuria at the time of biopsy were investigated by multiple regression analysis (Table 5). The final model to predict serum creatinine at the time of the biopsy included the extent of interstitial fibrosis, the percentage of glomeruli with collapsing lesions, and male gender (model $P = 0.0001$). Daily urinary protein excretion was best predicted by the extent of effacement foot processes and the patient's age (model $P = 0.0002$).

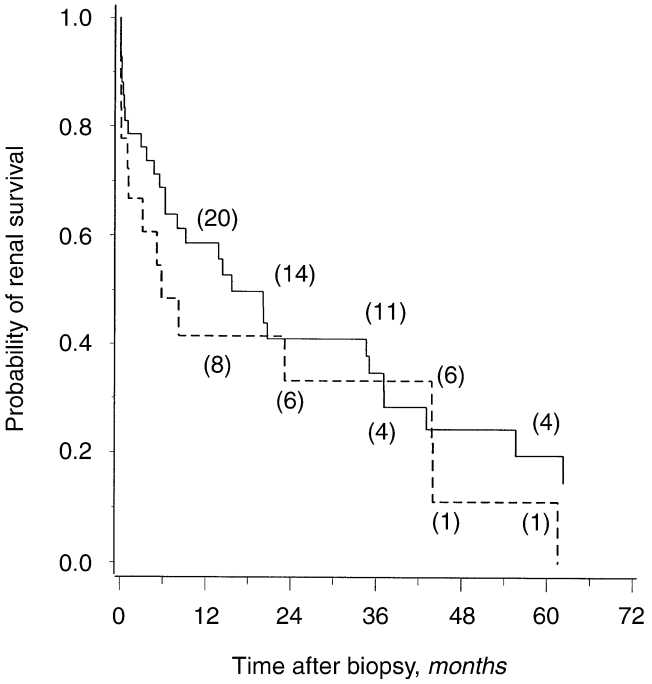

Fig. 1. Probability of renal survival of HIV (– – – –) and non-HIV patients (———) with collapsing glomerulopathy (CG). The number of patients remaining is shown in parentheses.

Clinical course and outcome

The duration of follow-up after the biopsy was 14.0 ± 18.6 months in HIV patients (range 0 to 62 months, median 5.5) and 21.4 ± 23.6 months in non-HIV patients (range 0 to 91 months, median 10.5), respectively (P = 0.24). During the follow-up period, 14 (77.8%) HIV and 30 (71.4%) non-HIV patients developed ESRD (P = 0.6). In the group of patients with functioning kidneys at the end of follow-up, serum creatinine >2.0 mg/dl was observed in 2 of 4 HIV and 6 of 12 non-HIV patients.

During the total follow-up period (including time on dialysis in some patients, median 16 and 36 months in HIV and non-HIV patients, respectively), nine HIV and seven non-HIV patients died. Most of the patients (7 HIV and 4 non-HIV) were on renal replacement therapy at the time of death, whereas two HIV and three non-HIV patients had variable degrees of renal insufficiency; however, the cause of death in these patients was not directly related to the complications of their renal disease. One HIV patient and eight non-HIV patients received a renal allograft. The recurrence of CG was diagnosed in one non-HIV patient six months after she received a living-related allograft from her son (this case was the subject of a case report) [23].

The significance of HIV status to predict renal survival was tested by product-limit analysis (18 HIV and 42 non-HIV patients). There were 44 events. Figure 1 shows that the time to renal death was not significantly different for HIV and non-HIV patients without accounting for other potentially predictive variables (P = 0.28). The product limit estimate for the median renal survival was 5.8 and 15.7 months in HIV and non-HIV patients, respectively. The estimated event rates at 24 months were 33 and 41% for HIV and non-HIV patients, respectively. A multiple variable model was developed to account simultaneously for potentially important clinical, demographic, and morphologic features. Potential predictors that were tested were patient's gender, age, race, risk for HIV, HIV status, interaction between HIV status and months after biopsy, time from manifestation of the disease to biopsy, serum creatinine at biopsy >2.0 mg/dl, proteinuria at biopsy >8.0 g/day, the percentage of glomeruli with collapsing lesions >20%, the percentage of globally sclerosed glomeruli >20%, the extent of active interstitial inflammation >20%, the extent of interstitial fibrosis >20%, the presence of tubular casts with microcystic dilation, and the presence of TRIs in endothelial cells. The final model shown in Table 6 significantly predicted renal death (P = 0.0001). This model shows that the risk of renal death was significantly increased by interstitial fibrosis >20%, serum creatinine >2.0 mg/dl, proteinuria > 8 g/day, and HIV infection and was decreased by a frequency of glomeruli with collapsing lesions >20%. Consideration of the HIV term and the interaction term together shows that the effect of HIV infection was to increase the risk of renal death nearly sixfold at biopsy, but this effect diminished during follow-up. In addition, interstitial fibrosis (P = 0.0001) and serum creatinine (P = 0.0008), as single predictors, were significantly associated with earlier renal death in product-limit analysis (Figs. 2 and 3).

Table 6. Cox model to predict renal survival in patients with CG

	Hazard ratio	95% confidence interval	P value
Model			0.0001
% Interstitial fibrosis *>20%*	7.48	(2.73, 20.52)	0.0001
Serum creatinine *>2.0 mg/dl*	5.79	(2.03, 16.48)	0.001
Proteinuria *>8 g/day*	2.95	(1.24, 6.98)	0.014
% Glomeruli with collapsing lesions *>20%*	0.26	(0.10, 0.65)	0.004
HIV infection	5.94	(1.68, 21.02)	0.0057
Interaction between HIV infection and time (*months*) after biopsy	0.92	(0.88, 0.97)	0.0005

Potential clinical, demographic, and pathological predictors of progression of renal failure, including HIV status, were also investigated by multiple regression analysis where the patient's slope of the reciprocal creatinine was used as the response variable. The rate of decline of renal function correlated significantly with daily proteinuria at biopsy (N = 33, P = 0.002), accounting for 27% of the variance.

Data on therapy were available on 37 non-HIV patients.

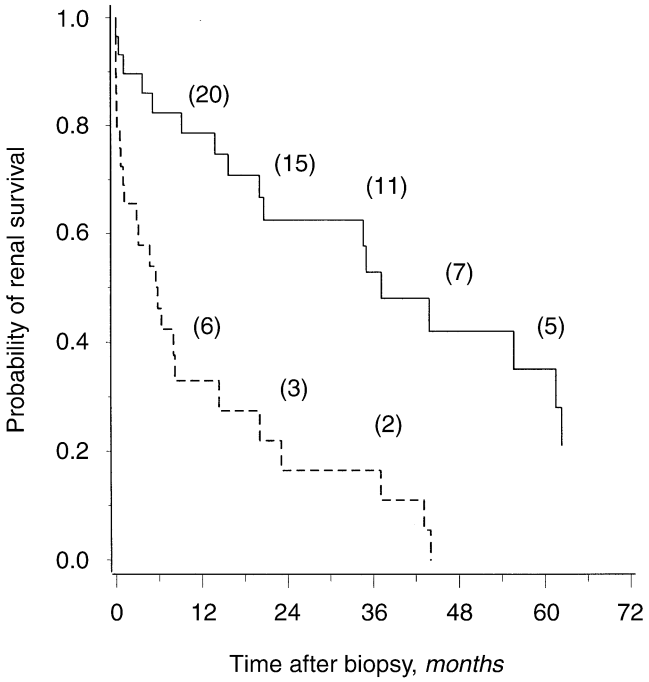

Fig. 2. Probability of renal survival of collapsing glomerulopathy (CG) patients with interstitial fibrosis >20% (– – – –) and ≤20% (———). The number of patients remaining is shown in parentheses.

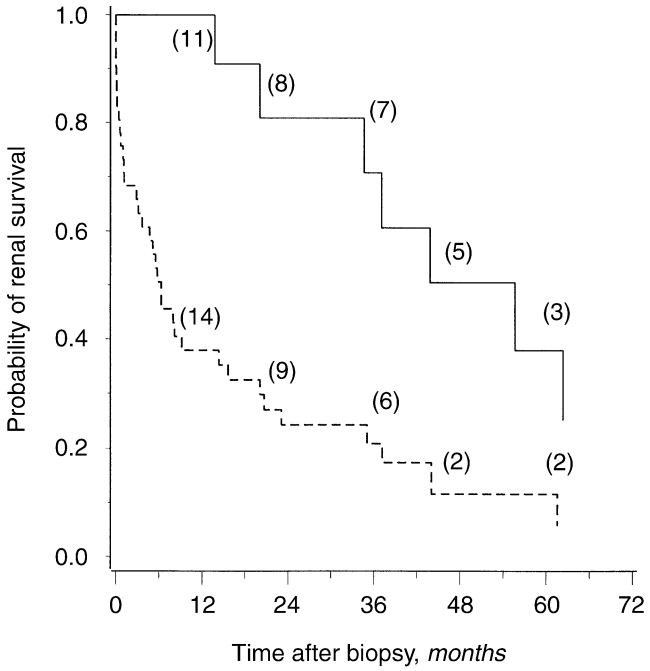

Fig. 3. Probability of renal survival of collapsing glomerulopathy (CG) patients with serum creatinine at the time of the biopsy of >2 mg/dl (– – – –) and ≤2 mg/dl (———). The number of patients remaining is shown in parentheses.

Twenty-three non-HIV patients were treated with steroids. Two of them responded well to the therapy and had normal renal function at the end of the follow-up period. Seven patients revealed partial response of their nephrotic syndrome or renal failure, as defined by the treating nephrologist (some became steroid-dependent). Only two of them had normal serum creatinine at the end of the follow-up, whereas one had chronic renal failure, and four patients had reached ESRD. Fourteen patients were steroid-resistant, and only three of them had some renal function remaining at the end of follow-up, however, with serum creatinine >2.0 mg/dl.

Six non-HIV patients also received cytostatic therapy, which, in general, did not seem to ameliorate their nephrotic syndrome, although two of these patients had normal serum creatinine at the end of follow-up, whereas all others developed ESRD. Three patients were also treated with cyclosporine A: Two of them did not respond to the therapy and developed ESRD. One patient developed "cyclosporine-dependent" nephrotic syndrome and a chronic renal failure.

Data on therapy were available on 15 HIV patients. Only two HIV patients received a short trial of steroids, with no definable effect. Seven patients received antiviral therapy for their HIV infection.

DISCUSSION

By review of our renal biopsy material, we were able to identify 18 HIVAN (HIV-associated CG) and 42 non-HIV CG cases diagnosed during the period from 1979 to the beginning of 1997. It seems meaningful that approximately two thirds of renal biopsies with this pattern of renal injury, once thought to be rather specific for HIV patients [8], were found in non-HIV patients. Furthermore, during the same period, CG was being increasingly recognized in non-HIV patients: only 6 of 18 HIVAN but as many as 39 of 42 non-HIV CG cases were diagnosed after 1989 (data not shown). This evidence is also in keeping with the notion of an increasing incidence of idiopathic CG [17]; however, this trend was not observed by others [18].

In our study, we applied a phenomenological approach to this relatively new clinicopathologic entity of CG in that morphologic evidence of CG and adequate information on the patient's HIV status were the only inclusion criteria for the study. This allowed us to include the whole spectrum of CG and to explore potential factors that contribute to the occurrence of this type of renal injury. In particular, we questioned whether CG that develops in HIV and non-HIV patients differs in terms of demographic, clinical, or pathological characteristics. Although previous studies showed idiopathic CG as being a more aggressive form of FSGS when compared with classic idiopathic FSGS [16–18], and HIVAN to have more severe pathologic changes than matched HAN and idiopathic FSGS controls [9], we report com-

parative clinicopathologic and follow-up data on 60 unselected CG patients with and without HIV infection.

A comparison of demographic, clinical, and pathological features of CG in HIV and non-HIV patients in our material revealed remarkable similarities. Patients' sex distribution, mean age, serum creatinine, daily proteinuria at biopsy, and most of the clinical manifestations at presentation or at the time of biopsy were indistinguishable. Moreover, the same can be said about the morphologic expression of the disease: The extent of the glomerular involvement by collapsing and sclerotic lesions as well as the extent of active and chronic interstitial disease was indistinguishable. Similarly, the probability of renal survival was not significantly different in HIV versus non-HIV patients by product-limit analysis without controlling for other variables.

Several features of CG, however, are clearly distinct in HIV and non-HIV patients. A high prevalence of blacks was found in the HIV group as opposed to an almost equal distribution in non-HIV patients. Not surprisingly, 72% of HIV patients had identified risk factors for HIV infection, whereas only 19% of non-HIV patients revealed potential risk factors for HIV. Five non-HIV patients had history of IVDA and could have been considered as having HAN, constituting only a small proportion of our non-HIV CG cases.

At presentation, the patients with CG rather frequently revealed flu-like illness with nonspecific respiratory and/or gastrointestinal symptoms. However, a history of fever was more frequently noted in HIV patients. As reported in patients with HIVAN [7], our HIV patients rarely presented with arterial hypertension (as defined by the treating nephrologists). The incidence of hypertension was significantly lower in HIV patients when compared with non-HIV patients (6 vs. 29% in non-HIV). However, considering that over 70% of all CG patients presented with a significant degree of renal failure, the discrepancy between the incidence of hypertension and the incidence of renal failure at presentation appears to exist in both groups of patients.

Only two pathological features of CG appeared with significantly different incidence in HIV and non-HIV patients. The presence of TRIs in glomerular endothelial cells was noted in 76% of HIV patients as compared with 29% of the non-HIV group. TRIs are thought to be a morphologic "footprint" of high levels of plasma alpha-interferon [24, 25] and have been found with high frequency in patients with HIV infection [26] and HIVAN [5, 9, 27] and, therefore, may serve as a marker of HIV infection. However, the frequency of TRIs (76%) in our HIV patients appears much less than reported previously in 92% of patients with HIVAN [9]. This relatively low frequency of TRIs in our HIV patients does not seem to be caused by "less sensitive" electron microscopy technique, as we were able to document TRIs in 29% of non-HIV patients with CG, whereas others have reported a very low incidence of these endothelial inclusions in idiopathic CG [16–18]. Because only one of five non-HIV patients with an evidence of HCV infection and IVDA had TRIs in the endothelial cells, the high frequency of TRIs in our non-HIV patients is not solely contributed by this subgroup of patients. In fact, the high frequency of TRIs in our non-HIV patients is also due to seven patients having associated systemic illnesses: SLE-like disorder (3 patients), mixed connective tissue disease (1 patient), acute monoblastic leukemia (1 patient), cerebral arteritis (1 patient), and HTLV-I infection (1 patient). A calculated positive predictive value of 0.54 TRIs for HIV infection in patients with CG is somewhat lower than suggested in previous reports [9, 27]. Interestingly, D'Agati and Appel suggested that TRIs are less abundant in cases of HIVAN diagnosed in the late 1990s [28]. The incidence of TRIs in our HIV patients, however, has not changed significantly before and after 1989 (data not shown). Marked cast nephropathy with microcystic tubular dilation was another pathological feature more frequently observed in HIV patients, a finding consistent with a previous observation [9].

One additional ultrastructural feature of CG is worth mentioning: Only 57% of HIV and 38% of non-HIV cases, respectively, were considered to have diffuse effacement of foot processes (over 80% of glomerular capillary surface). It is our impression that the effacement of foot processes in this condition is less extensive than in minimal change disease, in spite of the high level of proteinuria. Nevertheless, the extent of "fusion" of the foot processes was the best predictor of proteinuria in our multiple regression analysis. Of note, two previous studies on idiopathic CG have also characterized the degree of effacement as "various" [16] or "mean 80%" of the capillary surface [17]. This peculiarity may be a reflection of a qualitatively different pathophysiological mechanism of podocyte injury in CG when compared with minimal change disease, as recently suggested by others [29, 30].

A comparison of our non-HIV patients with CG with the data from previous studies of idiopathic CG [16–18] is presented in Table 7. In general, there is concordance in all major parameters of our non-HIV CG patients and idiopathic CG, although our patients seem to have clinically somewhat more severe disease and were biopsied earlier when compared with the largest of the published series [17]. We found the lowest prevalence of blacks (57%), although still comparable to that of 61%, in New York City [17]. In contrast to the previous studies [16–18, 31], a slight predominance of females in the group of non-HIV CG is seen. Importantly, a similar prevalence of female gender is seen in our HIV patients, in contrast to the previous reports on HIVAN [1, 3, 9], whereas a high prevalence of blacks in HIV CG is con-

Table 7. Non-HIV CG in the context of idiopathic CG

	Present study	Valeri et al [17]	Haas et al [18]	Detwiler et al [16]
N of patients	42	43	21	16
Gender % *male*	45[a]	58	62[a]	69[a]
Race % *black*	57	61	86	81[a]
Mean age *years*	37.8 ± 14.2	32.2	30.4 ± 9.9	41.4 ± 19.1
Mean time to biopsy *months*	2.3 ± 2.7	7.9		
Proteinuria *g/day*	13.3 ± 10.6	10.2	14.3 ± 9.6	13.2 ± 7.7
Mean serum creatinine at biopsy *mg/dl*	5.4 ± 5.3	4.2	3.8 ± 2.7	3.5 ± 3.4
Glomeruli with collapsing lesions *mean* %	41	52		
Globally sclerosed glomeruli *mean* %	21	17		
Marked tubular microcysts %	40	12		
TRI %	29	5[a]	0[a]	6[a]

[a] Recalculated from original data for purposes of comparison

cordant. Therefore, our data suggest that HIVAN is a "disease of blacks" rather than "black males," as considered previously [32]. Similar to previous suggestions that HIVAN is not caused by IVDA *per se* [4, 32, 33], we confirmed that only a portion of our HIV patients (44%) and non-HIV patients (12%) had a history of IVDA. Interestingly, all five non-HIV intravenous drug abusers with CG on biopsy (that could also be considered as HAN) tested positive for HCV (3 of them before the biopsy or dialysis). In other words, a small subgroup of our non-HIV CG patients might be interpreted as having HAN, and all of them were found to be HCV positive. Recently, a high frequency of HCV infection in intravenous drug users with FSGS has been reported [34]. These results are also in keeping with a recent report [35] that indicated a sharp decrease in the incidence of new cases of HAN as a cause of ESRD in New York City since 1989. The lack of FSGS in European intravenous drug addicts [36] and a high prevalence of this form of glomerular injury in African American addicts [37–39] raises the possibility that HAN has a stronger pathogenic link to the black race (and possibly to HCV infection) than IVDA *per se.* Similarly, the occurrence of HIVAN in HIV patients was initially attributed to factor of IVDA; however, later observations proved this relationship to be caused by high prevalence of blacks HIVAN [4, 11, 33]. It is likely that patients diagnosed as HAN in the past are indeed patients with CG diagnosed during the late, progressive phase of the disease.

In contrast to previous studies on idiopathic CG [16–18], a significant proportion of our non-HIV patients had serious concurrent medical conditions. Five black females manifested a SLE-like disorder (2 of them died because of their systemic illness), an association not previously reported. Another five non-HIV patients had positive ANA tests at titers higher than 1:40; thus, 10 (32%) of our non-HIV patients had positive ANA when tested. In previous reports, only two CG patients were positive by antinuclear antibody test, and one patient had a lupus-like syndrome [16, 17]. Four other patients suffered from mixed connective tissue disease, granulomatous cerebral arteritis, multiple myeloma, or acute monoblastic leukemia. Interestingly, all of these conditions appear to have a common denominator: a major disturbance of the immune system. In addition, at least three other non-HIV CG cases are associated with evidence of HCV infection and one case with HTLV-I infection. Thus, of the 42 non-HIV cases, 9 are associated with autoimmune conditions or hematological neoplasia, and 4 had established viral infections other than HIV-1 or HIV-2. In other words, as many as 31% of patients with "idiopathic" CG appear to have important comorbidity in our material.

Data on HLA antigen frequencies in patients with CG have not been reported. Although we observed a relative increase in frequencies of HLA-B18 and DR-10 in blacks and B44 and DR4 in whites, a larger set of observations is required to test the statistical significance of these findings.

The probability of renal survival during the follow-up period was not significantly different overall in HIV and non-HIV patients by product-limit analysis, although a tendency of worse prognosis of the renal disease in HIV patients can be noted. Multiple Cox regression analysis, however, revealed a time-dependent effect of HIV infection on renal survival. Namely, the probability of renal death was significantly higher in HIV patients at the time of the biopsy, but this difference diminished in the perspective of long-term prognosis. Indeed, the pattern of renal survival curves (Fig. 1) illustrates this effect, with the probability of renal survival becoming similar in HIV and non-HIV patients after two years of follow-up. It is difficult to speculate on the causes of this time-dependent effect, which can also be expressed as a beneficial effect of being HIV negative. It is likely that this difference in survival is due, at least in part, to differences in the therapeutic approach to these patients. Although 62% of our non-HIV patients were treated with steroids (with variable effect, though), only 13% of HIV patients received a short trial of steroids. Because steroid therapy has been shown to have a beneficial effect on renal function and proteinuria in some patients with HIVAN [40–43]

and has been associated with a full or partial response in 24% of our non-HIV patients, one might expect that steroid therapy could have slowed the development of ESRD in the non-HIV group. Although our data on the effect of steroid therapy in non-HIV patients are not encouraging, we observed a slight but nonsignificant beneficial effect of steroid therapy on renal survival in our non-HIV patients (data not shown). On the other hand, the probability of renal survival became quite similar in HIV and non-HIV patients when patients treated with steroids were excluded from the analysis (data not shown). Interestingly, a review of individual serum creatinine curves over time in 29 of our patients with an adequate number of creatinine values revealed a particular pattern of progression of renal insufficiency in 12 patients (1 patient with HIV). This pattern is characterized by a high degree of renal failure (serum creatinine >2 mg/dl) at the time of the biopsy, with a subsequent partial but substantial improvement of the serum creatinine to levels below 2 mg/dl over a few months. This sometimes spontaneous recovery (discussed later in this article) was followed by eventual progression to ESRD or a significant degree of chronic renal failure over several months or years. Nine of these 12 patients were treated with steroids, but 3 of the 12 patients (1 patient with HIV infection) showed this course without therapy. A similar pattern of improvement and subsequent progression has been reported in a patient with HIVAN treated with steroids [43]. It appears that a subgroup of patients with CG presents with an acute phase that is more likely to benefit from steroid therapy, as suggested previously in HIVAN [42], followed by remission and eventual progression to ESRD. Whether this course represents a natural history of CG or is a modification of the latter because of therapeutic interventions remains unresolved. The spontaneous remission of the renal failure in some patients with CG should be taken into account when evaluating the potential beneficial effect of different therapeutic regimens on the course of the disease.

Renal survival in our HIV patients with CG seems somewhat better than previously reported for HIVAN [1, 3, 6, 10]. The relatively short time from manifestation of renal disease to biopsy, asymptomatic stage of the HIV infection in a great proportion (up to 67%) of our patients at biopsy and, potentially, improved management of HIV patients may all have contributed to this difference [6, 44]. We did not observe, however, a significant improvement of renal survival in those HIV (and non-HIV) patients diagnosed after 1989 (data not shown).

Renal survival of the non-HIV group is similar to that previously reported in idiopathic CG [16–18]. The median survival of our non-HIV patients was 16 months compared with 13 months in a previous study [17]. Again, a shorter duration of the disease before the biopsy in our patients has to be taken into account in assessing renal survival curves.

In general, our study confirms a poor prognosis of CG. The unfavorable outcome is also demonstrated by the observation that half of the patients without ESRD often had pronounced renal insufficiency at the end of the follow-up period, and 16 patients died, 5 of them before developing ESRD. In addition, our data indicate the possibility of recurrence of the disease in the allograft, as reported previously by other authors [16, 23, 31, 45, 46].

We were able to develop a highly significant Cox model for the prediction of renal survival in patients with CG. Along with the time-dependent effect of HIV infection discussed earlier in this article, extensive interstitial fibrosis (>20% of cortical area), high serum creatinine (>2 mg/dl), and high proteinuria (>8 g/day) were risk factors for renal death. These predictors can be considered "classic" in nephrology, interstitial fibrosis representing chronic irreversible loss of renal parenchyma, whereas proteinuria can be interpreted as a measure of activity of the glomerular disease process. Serum creatinine in CG may reflect both chronic irreversible loss of renal function and potentially reversible renal failure during the acute phase of the disease (as discussed earlier in this article); indeed, serum creatinine correlated with both the extent of interstitial fibrosis and the frequency of glomerular collapse in our multiple regression analysis. The positive effect of the extensive collapsing lesions (>20% glomeruli) on renal survival in this multiple Cox model could be interpreted as suggestive that patients with these acute lesions may have an acute, partially reversible form of renal injury and functional impairment. Of note, the extent of collapsing lesions was not a significant predictor of renal death by product-limit analysis (data not shown). Importantly, the patient's race and gender were not found to predict renal survival in our patients. This means that despite possible race and gender predisposition to CG, this condition has a bad prognosis, regardless of sex and race.

The rate of decline of renal function following the renal biopsy, measured as a slope of the reciprocal serum creatinine, was best predicted by the degree of daily proteinuria at time of the biopsy, whereas the latter parameter best correlated with the extent of effacement of podocyte foot processes.

In summary, we found that CG represents a clinicopathological entity with poor prognosis. It may develop in patients with HIV and other viral infections as well as in the course of autoimmune and hematological disorders. Although CG in HIV and non-HIV patients reveals indistinguishable clinicopathological features, a high prevalence of black race, TRIs in the glomerular endothelial cells, and marked cast nephropathy are more characteristic of HIV-associated CG. The probability of renal sur-

vival was significantly lower in HIV patients with CG in only the early phase of the follow-up period.

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APPENDIX

Abbreviations are: AIDS, acquired immunodeficiency syndrome; CG, collapsing glomerulopathy; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HAN, heroin-associated nephropathy; HBsAg, hepatitis B-s-antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIVAN, HIV-associated nephropathy; IVDA, intravenous drug abuse; TRI, tubuloreticular inclusion.

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